Metabolic Health Matters:

Breastfeeding on the

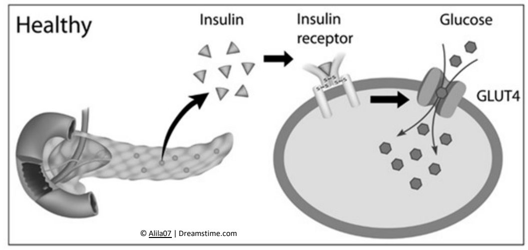
Insulin Resistance Spectrum

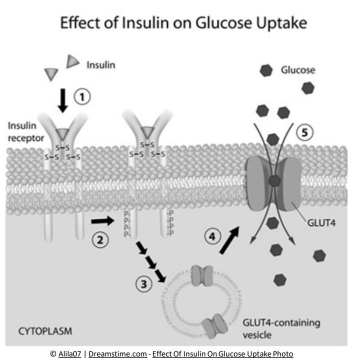
~No disclosures of financial or other conflicts of interest~

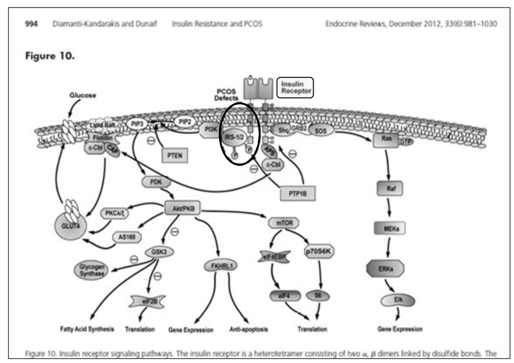
© 2021 Lisa Marasco, MA, IBCLC, FILCA

LisaIBCLC@Marasco.US

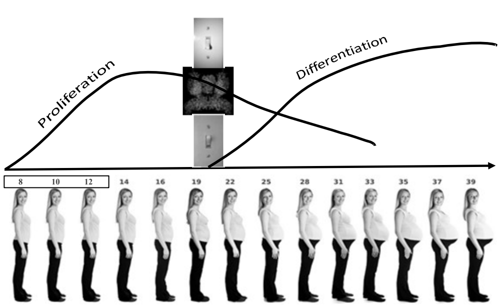
Normal insulin dynamics





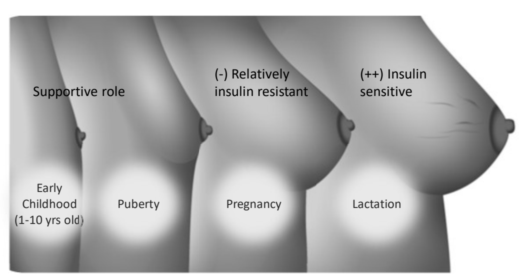


Insulin regulates transitional switch



Neville, M. C., Webb, P., Ramanathan, P., Mannino, M. P., Pecorini, C., Monks, J., . . . MacLean, P. (2013). The insulin receptor plays an important role in secretory differentiation in the mammary gland. *Am J Physiol Endocrinol Metab, 305(9), E1103-1114.*

Insulin and Mammary development



Insulin: Crucial member of the Lactogenic Complex

Insulin

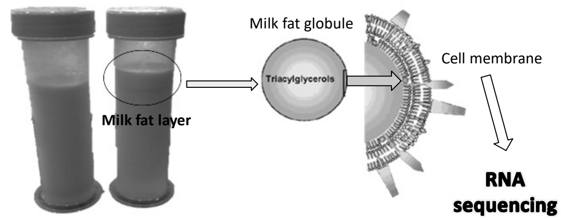
Lactogenesis II

Prolactin

Cortisol

The Lactogenic Complex

Findings about stages of lactation



Lemay, DG…Nommsen-Rivers, L. A. (2013). RNA Sequencing of the Human Milk Fat Layer Transcriptome Reveals Distinct Gene Expression Profiles at Three Stages of Lactation.

Identifying the changes in stages

	Colostrum →	Transitional Milk →	Mature Milk
Stages defined by Na/K ratio, (tight junction closure) not day PP	> 2.0	<2 - .6	< .6
Major expressed genes	FTL (ferritin) CTSD (cathepsin D)	LALBA (α-Lactalbumin) CSN2	CSN2 (β-casein) LALBA (α-Lactalbumin) = ~45%
Priority of gene expression	Immune defense	*Massive development of protein synthesis infrastructure *Inhibition of protein degradation	*Massive synthesis of lipids
Cell cycle genes	↑ regulated		↓ regulated
Immune response genes	↑↑↑	↑↑	↑
Lipid biosynthesis genes	↑	↑↑	↑↑↑

Lemay, D. G., Ballard, O. A., Hughes, M. A., Morrow, A. L., Horseman, N. D., & Nommsen-Rivers, L. A. (2013). RNA Sequencing of the Human Milk Fat Layer Transcriptome Reveals Distinct Gene Expression Profiles at Three Stages of Lactation. *PLoS One, 8(7). http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0067531*

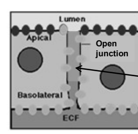
What is (or isn't) happening inside the breast? Sodium tells the story…

Sodium changes did not line up with days after birth!

Colostrum stage
Na:K > 2.0

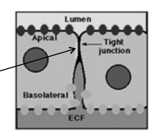
Transitional milk
Na:K < 2 - .6

Mature Milk stage
Na:K < .6



Sodium passes to milk easily

Sodium cannot pass easily



Lemay, D. G., Ballard, O. A., Hughes, M. A., Morrow, A. L., Horseman, N. D., & Nommsen-Rivers, L. A. (2013). RNA Sequencing of the Human Milk Fat Layer Transcriptome Reveals Distinct Gene Expression Profiles at Three Stages of Lactation. *PLoS One, 8(7). http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0067531*

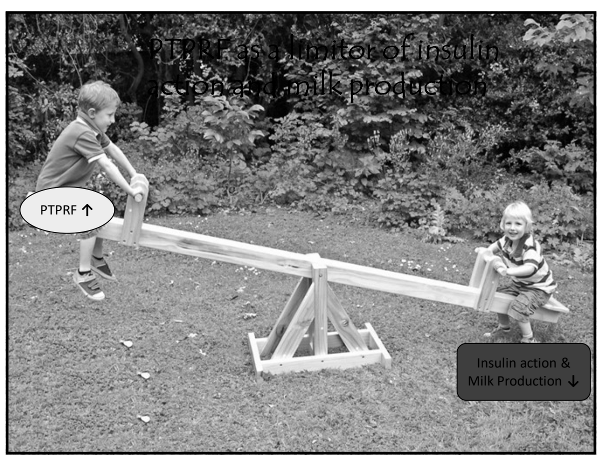
Insulin dynamics change with stages

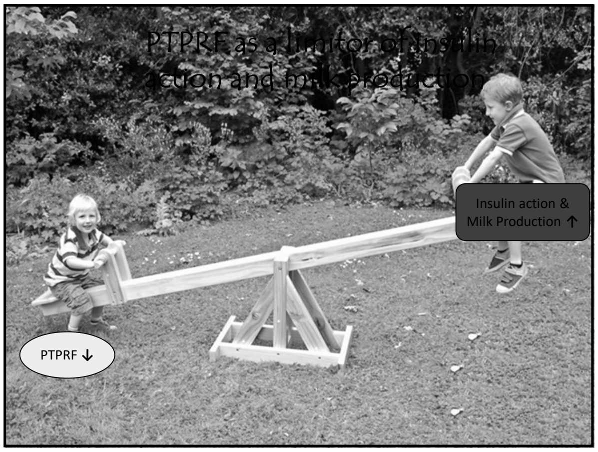
Colostrum → Transitional Milk	Transitional → Mature Milk
Strong modulation of insulin signaling *Breast becomes sensitized to insulin*	Insulin signaling maintains steady-state *Robust expression.*
Up-regulation of lipogenesis, protein synthesis	**Toning down** of initial steep up-regulation of metabolic signals via **up-regulation** of **PTPRF**, which suppresses insulin action
Inhibition of apoptosis, glycolysis and glycogenesis	
PTPRF ↑	**PTPRF ↓**

PTPRF = protein tyrosine phosphatase, receptor type F

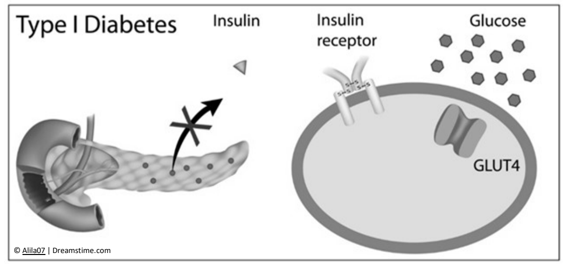
Insulin necessary for milk protein synthesis

Lemay, D. G., Ballard, O. A., Hughes, M. A., Morrow, A. L., Horseman, N. D., & Nommsen-Rivers, L. A. (2013).

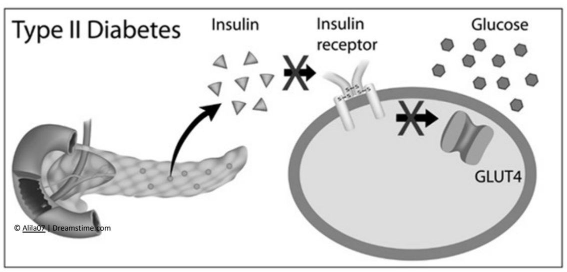




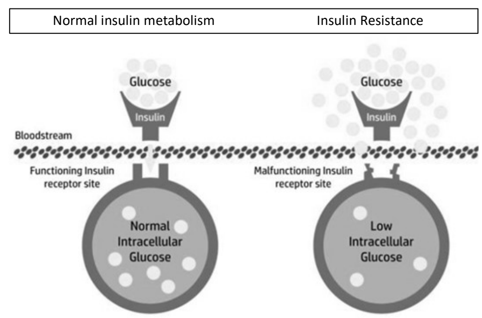
Insulin & Diabetes: Type 1



Insulin & Type 2 Diabetes

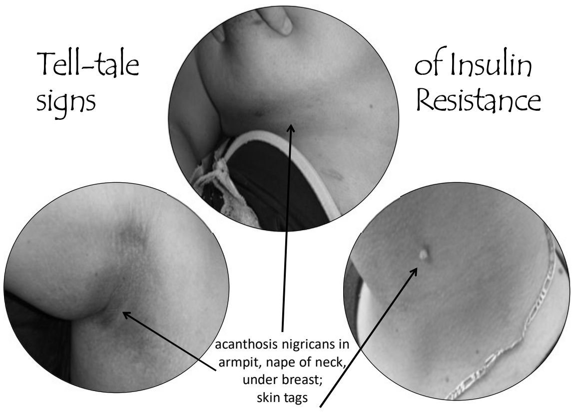


Type 2 & Gestational Diabetes



→ Compensatory *hyperinsulinemia*

Tell-tale signs of Insulin Resistance

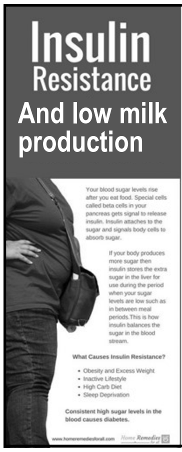


How IR can affect production

Markers	Mature Group 1	Mature Group 2
Median onset of notably fuller breasts	34 hrs	74 hrs
Insulin secretion	Above median	Below median
Insulin sensitivity	Above median	Below median
Expression of PTPRF	_baseline_	Significantly higher than Group 1 (over-expressed)
Milk Production	Engorgement peaked day 4-5, then down regulated to demand	

Lemay, D. G., Ballard, O. A., Hughes, M. A., Morrow, A. L., Horseman, N. D., & Nommsen-Rivers, L. A. (2013). RNA Sequencing of the Human Milk Fat Layer Transcriptome Reveals Distinct Gene Expression Profiles at Three Stages of Lactation. *PLoS One, 8(7).*

CONCLUDING HYPOTHESIS: *"Women with decreased insulin sensitivity will experience a more sluggish increase in milk output in response to infant demand as a result of PTPRF over-expression in the mammary gland"*



48 mothers 1-8wks pp w/low supply

33 had signs of IR → BMI ~37 → Milk production median **216** [158-332]

15 non-IR → BMI ~25 → Milk production median **377** [294-598]

"Additional deficit associated w/ IR"

Nommsen-Rivers, et al. (2017). Milk Production in Mothers with and without Signs of Insulin Resistance. *The FASEB Journal*

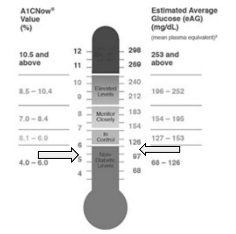
Glover (2017). *Impact of metabolic dysfunction on breastfeeding outcomes in GDM*

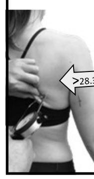
Table. Associations between metabolic markers and breastfeeding duration in GDM

Metabolic marker tertiles	Time to weaning MV-adj HR (95% CI)	Wald chi square p value	Undesired weaning, N (%)	M-H Chi Square p
Fasting glucose, mg/dL		**.04**		**.04**
<93	1.0 (ref)		5 (21.7)	
93-101	.77 (.33-1.83)		6 (23.1)	
>101	1.84 (1.11-3.06)		12 (48.0)	
Hemoglobin A1c		**.01**		NS
<5.3	1.0 (ref)		5 (21.7)	
5.3-5.6	1.45 (0.87-2.41)		10 (38.5)	
> 5.6	2.51 (1.36-4.60)		10 (34.5)	
Body Mass Index, kg/m2		**<.01**		**<.01**
<34	1.0 (ref)		6 (20.7)	
34-40.6	1.22 (.77-1.94)		6 (21.4)	
>40.6	2.21 (1.24-3.94)		14 (56.0)	
Subscapular skin fold, mm		**<.0001**		**.04**
<28.3	1.0 (ref)		6 (21.4)	
28.3-33.0	3.66 (2.62-5.11)		10 (34.5)	
>33.0	2.82 (1.57-5.06)		10 (40.0)	

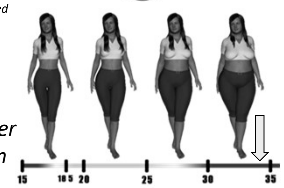
NS = not significant

Risk of reporting not breastfeeding as long as desired

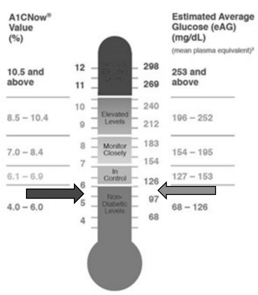




A1C, BMI, OGTT & subscapular were associated w/ shorter duration of lactation



Confirmed by Verd 2016



Compared women with *normal* 1-hr glucose challenge tests (<7.8 mmol/L) with those who had *elevated* 1-hr test (≥ 7.8mmol/L but <10.6 mmol/L) but clinical indices below threshold for GDM diagnosis

Results: *Mildly impaired women abandoned exclusive breastfeeding sooner than non-impaired:* OR 1.65

Breastfeeding in women with GDM

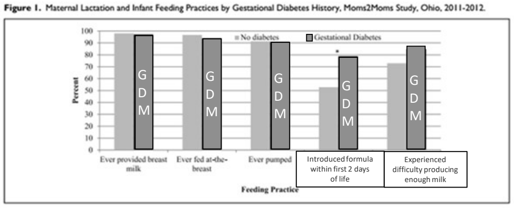
	Any Bfg Rate	Duration: Full Bfg	Duration: Any Bfg
Healthy = 527	86%	17 wks	
GDM all = 257	75%	9 wks	
GDM-Diet		12 wks	20 wks
GDM Insulin		4 wks	10 wks
GDM + BMI <30	80%		17 wks
GDM + BMI >30	65%		12 wks

Conclusions: *Mothers with gestational diabetes, especially mothers with insulin-dependent gestational diabetes, and obese mothers breastfed their children significantly less and for a shorter duration than healthy mothers.*

Breastfeeding in women with gestational diabetes Hummel, S., Hummel, M., Knopff, A., Bonifacio, E., & Ziegler, A. G. (2008).

GDM mothers start the same but supplement sooner

Figure 1. Maternal Lactation and Infant Feeding Practices by Gestational Diabetes History, Moms2Moms Study, Ohio, 2011-2012.



*P < .05. Oza-Frank, et al. (2016). **Early Lactation and Infant Feeding Practices Differ by Maternal Gestational Diabetes History**. *J Hum Lact.*

Table 3. Infant Age in Days of Initiation of Maternal and Infant Feeding Practices by Gestational Diabetes History, Moms2Moms Study, Ohio, 2011-2012.[a]

Variable	No Diabetes (n = 398)	Gestational Diabetes (n = 34)	P Value
At-the-breast, median (IQR)	1.0 (1-1)	1.0 (1-1)	.22
Pumping, median (IQR)	7.0 (2-21)	3.0 (1-14)	< .05
Formula feeding, median (IQR)	4.0 (1-90)	1.0 (1-2)	< .01

Abbreviation: IQR, interquartile range.
[a]Each comparison by diabetes status was made using the Wilcoxon-Mann-Whitney test.

GDM meds (A2) vs GDM diet (A1)

TABLE 3. FREQUENCIES AND UNADJUSTED AND ADJUSTED ODDS RATIOS OF BREASTFEEDING INITIATION AND CONTINUATION IN PATIENTS WITH A2 COMPARED WITH A1 GESTATIONAL DIABETES MELLITUS

	A2 GDM	A1 GDM	OR	aOR[a]
Any breastfeeding at hospital discharge	228 (76.3)	242 (80.4)	0.78 (0.53–1.16)	0.72 (0.44–1.16)
Exclusive breastfeeding at hospital discharge	86 (28.9)	115 (38.2)	0.66 (0.47–0.92)	0.83 (0.54–1.28)
Any breastfeeding at 3 months postpartum	237 (84.3)	253 (87.5)	0.77 (0.47–1.24)	0.63 (0.34–1.17)
Exclusive breastfeeding at 3 months postpartum	40 (13.9)	77 (26.6)	0.44 (0.28–0.68)	0.58 (0.34–1.01)
Continued exclusive breastfeeding to 3 months postpartum	40 (13.9)	77 (26.6)	0.42 (0.22–0.79)	0.59 (0.25–1.39)

Categorical data are *N* (%).
[a]Adjusted for age, parity, BMI, and neonatal hypoglycemia.
aOR, adjusted odds ratio; OR, odds ratio.

*Study performed at a racially, ethnically and socioeconomically diverse academic medical center
*Treatment type considered proxy for severity of GDM
*Most common treatment for institution was insulin

	Rhode Island all	RI Study- all
Excl Bfg @ 2 days	64.5%	33.6%
Excl Bfg @ 3 moos	45%	20.3%

Kole-White et al. (2021). Breastfeeding Success Among Women with Gestational Diabetes Managed by Diet Only Compared with Those Requiring Medications. *Breastfeed Med*

Risk factors for Delayed Lactation with GDM: Who's at risk?

Matias 2014; Chapman 2014; Riddle 2016

Matias 2014 GDM statistics:

N=883 Racially and ethnically diverse population

One-third of GDM mothers experienced delayed onset of lactogenesis

Matias et al. (2014). Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus.

GDM Risk factors for lactation problems

Maternal Obesity:
AOR 1.56

Matias et al. (2014). Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus.

GDM risk factors

Insulin treatment during pregnancy:
AOR 3.11

Another interesting study….

Diabetes type	Any bfg discharge	Full bfg discharge	Any bfg 4 mo	Full bfg 4 mo
Type 1	93%	72%	61%	49%
Type 2 (pregestational)	86%	45%	34%	23%

Standard practice:

- Insulin-controlled during pregnancy
- Infants automatically given mother's milk or Nutramigen by cup or NG tube starting after first bfd/within 2 hrs & q3hrs first 24 hrs

Herskin, C. W., Stage, E., Barfred, C., Emmersen, P., Ladefoged Nichum, V., Damm, P., & Mathiesen, E. R. (2015). Low prevalence of long-term breastfeeding among women with type 2 diabetes. *J Matern Fetal Neonatal Med, 1-6. doi:10.3109/14767058.2015.1092138*

Implications!

"Women with GDM who are on insulin therapy have a delay in the onset of lactation, which suggests that insulin treatment may have adverse effects on milk production or composition in humans."

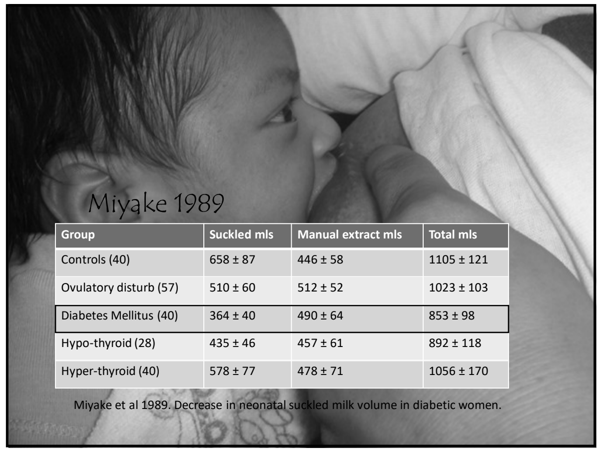
– Lee and Kelleher 2015

GDM risk factors

L	Latch
A	Audible swallowing
T	Type of nipple
C	Comfort (breast/ nipple)
H	Hold (positioning)

LATCH Score <7.5

Matias et al. (2014). Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus.



Miyake 1989

Group	Suckled mls	Manual extract mls	Total mls
Controls (40)	658 ± 87	446 ± 58	1105 ± 121
Ovulatory disturb (57)	510 ± 60	512 ± 52	1023 ± 103
Diabetes Mellitus (40)	364 ± 40	490 ± 64	853 ± 98
Hypo-thyroid (28)	435 ± 46	457 ± 61	892 ± 118
Hyper-thyroid (40)	578 ± 77	478 ± 71	1056 ± 170

Miyake et al 1989. Decrease in neonatal suckled milk volume in diabetic women.

Immature sucking patterns

		# sucks/ 5 min	Number of bursts	Interburst width (sec)
Term infants born to moms w/ GDM N=47 vs Controls	Controls N=55	157 +/- 73	19.7 +/- 7.9	8.6+/- 4.2
	Diet controlled N= 31	152 +/- 71	18.3 +/- 6.6	8.7+/- 4.6
	Insulin-managed N=16	115 +/- 65	14.5 +/- 6.5	11.5 +/- 7.5

Bromiker et al. (2006). Immature sucking patterns in infants of mothers with diabetes. *The Journal of pediatrics, 149(5), 640-643.*

The HyperInsulinemia-Androgen connection

Insulin resistance → Increased insulin → ↓ SHBG production in liver; ↑ Ovarian androgens → More free androgens → Interference w/removal of insulin by liver → Insulin resistance

Vicious Cycle

Schuring et al. Androgens and Insulin- Two Key Players in Polycystic Ovary Syndrome. *Gyn Geb Rundsch* 2008; 48:9-15.
Carlsen, S. M., & Vanky, E. (2010). Metformin influence on hormone levels at birth, in PCOS mothers and their newborns. *Hum Reprod, 25(3), 786-90.*

Androgens vs estrogens in the breast

Estrogen stimulates development of mammary tissue

E↑ E↑ T↓ T↓↓

Androgens slow growth of mammary tissue (possibly by ↓ERα)

Labrie F. Dehydroepiandrosterone, androgens and the mammary gland. Gynecology Endocrinology 2006; 22(3):118-30.

IR influence on pubertal mammary growth

Adult

High insulin levels *soon after* puberty → May *reduce* breast size & lactational capacity via androgens

Puberty

Insulin resistance *before* puberty → Can *decrease* overall glandular tissue inside (IGT)

High insulin levels *before* puberty → Can *increase* breast *size* (hypertrophy)

Fetal

Thanks to R. Craig, MD

Cassar-Uhl, D., & Liberatos, P. (2017). *Influence of adolescent and pre-pregnancy maternal weight status on lactation capability. Paper presented at the APHA 2017 Annual Meeting & Expo (Nov. 4-Nov. 8).*

Hyperandrogenism has been implicated in…

- ✓ Pre-eclampsia (Serin, 2001)
- ✓ Infant growth restriction (Carlsen, 2006)
- ✓ Increased mastopathies (Volobuev, 1990)
- ✓ More pregnancy complications (Palomba, 2009)
- ✓ Decreased prolactin (Aisaka 1984)
- ✓ Decreased lactation (Carlsen 2010, Aisaka 1984)
- ✓ Delayed lactation (Hoover, 2002; Betzold, 2004)

Androgens in pregnancy Carlsen 2010

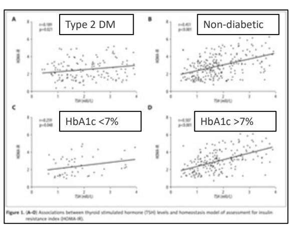
Negative breastfeeding association

		Testosterone	Androstenedione	Free T Index	DHEA
Controls: *Random selection*	3 & 6 mos	✓	✓	✓	
Blood drawn @ 25wks gestation					
Experimental: *Women at risk of SGA infant*	3 wks & 6 mos				✓

"Mid-pregnancy androgen levels are negatively associated with breastfeeding"

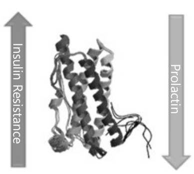
More significant IR impacts

TSH positively associated with insulin resistance

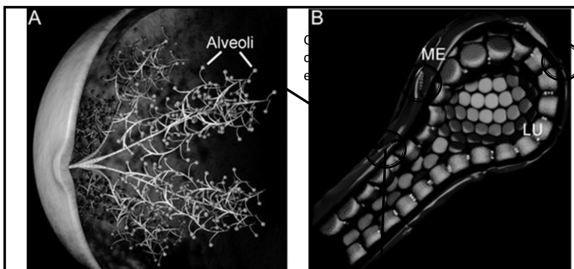


Zhu, P., Liu, X., & Mao, X. (2018). Thyroid-Stimulating Hormone Levels Are Positively Associated with Insulin Resistance.

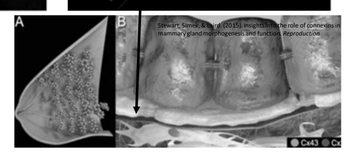
Higher IR associated with lower prolactin



Ponce et al. (2020). Low prolactin levels are associated with visceral adipocyte hypertrophy and insulin resistance in humans.

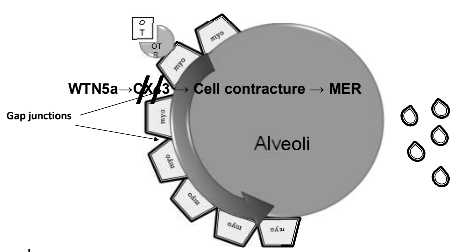


Cx-43: *another possible consequence of diabetes/hyperglycemia*



Mitasikova, M et al (2009) Diabetes and thyroid hormones affect connexin-43 expression in rat heart atria..

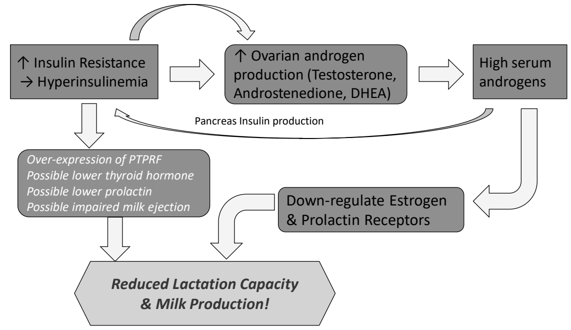
What happened with the CX-43 mutant?



Normal:
Oxytocin production → oxytocin release → bind to oxytocin receptor → WTN5A regulation of CX43 → cell contracture → milk ejection

Plante et al. (2010). Milk secretion and ejection are impaired in the mammary gland of mice harboring a Cx43 mutant while expression and localization of tight and adherens junction proteins remain unchanged. *Biol Reprod*

The broader picture of IR & Lactation



Thanks to R. Craig, MD

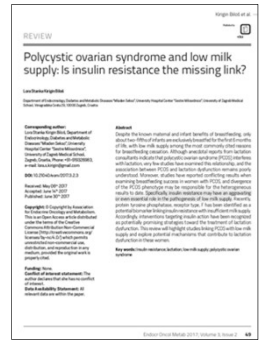
Impact of excessive weight gain in pregnancy

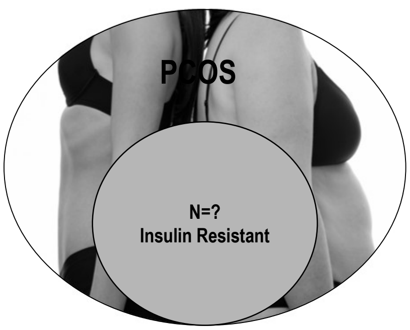
High BMI + excessive wt gain = additive risk for early termination of exclusive bfg

Hilson 2006	IOM	< IOM odds ratio	Within odds ratio	> IOM odds ratio
Overweight BMI 26-29	15-25 lbs	2.96	1.47	1.62
Obese BMI > 29	13-20 lbs	1.81	1.84	2.89

IOM = *Institute of Medicine*

What about PCOS?





Riddle & Nommsen-Rivers 2017:
"PCOS as a risk factor for insufficient lactation may be limited to the subset of women with postpartum glucose intolerance"

Case Study

McGuire, E., & Rowan, M. (2015). PCOS, breast hypoplasia and low milk supply: A case study. *Breastfeeding Review, 23(3), 29-32.*

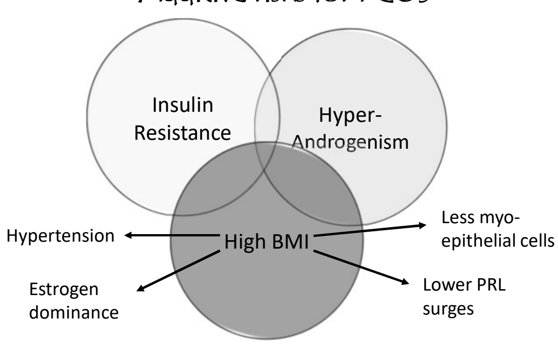
-Measured output via infant transfer = 52mls/day

-Did *not* respond to domperidone @ 30 or 60mg

-Clinical indications of insulin resistance

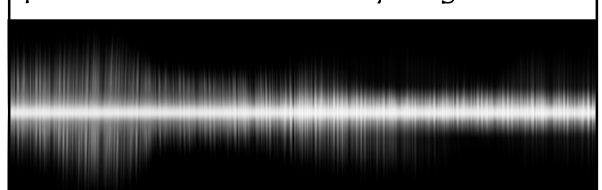
Metformin: Transfer *increased 69%* to 88mls/day

Additive risks for PCOS



Harrison 2016 Expert Opinion: *Obesity & PCOS status exacerbate breastfeeding continuation*

Breastfeeding is important for parents with insulin dysregulation!



On the positive side…

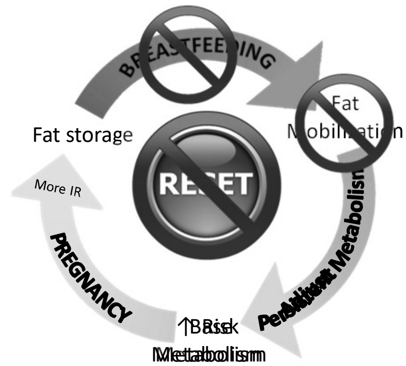
Gunderson 2014: Higher intensity of lactation was associated with improved fasting glucose and lower insulin levels at 6-9 weeks postpartum

> 4 mos of breastfeeding:

- ✓ Risk of Type 2 ↓ 25-35%
- ✓ More favorable metabolic profile

>12 mos breastfeeding:
Predicted less worsening of IR and fasting glucose at 3 years postpartum - *Bajaj 2016*

Breastfeeding is important! *Reset theory*



Stuebe, A. M., & Rich-Edwards, J. W. (2009). The reset hypothesis: lactation and maternal metabolism.

Longer lactation, less metabolic syndrome

LACTATION DURATION AND INCIDENT METABOLIC SYNDROME

TABLE 3
Cumulative incidence of the metabolic syndrome during follow-up intervals by GDM status and among duration of lactation categories (1986–2006)

Duration of lactation	Year 0–7	Year >7–10	Year >10–15	Year >15–20
Non-GDM births (all)	8/382 (2.1)	13/463 (2.8)	30/515 (5.8)	46/463 (9.9)
0–1 month	5/143 (3.5)	6/147 (4.1)	14/124 (11.3)	15/93 (16.1)
>1–5 months	2/101 (2.0)	3/126 (2.4)	6/131 (4.6)	11/120 (9.2)
6–9 months	1/89 (1.1)	3/114 (2.6)	5/132 (3.8)	9/121 (7.4)
>9 months	0/49 (0.0)	1/76 (1.3)	5/128 (3.9)	11/129 (8.5)
GDM births (all)	6/43 (14.0)	5/53 (9.4)	3/61 (4.9)	9/55 (16.4)
0–1 month	4/16 (25.0)	2/12 (16.7)	1/10 (10.0)	5/9 (55.6)
>1–5 months	1/8 (12.5)	1/15 (6.7)	0/13 (0.0)	2/13 (15.4)
6–9 months	1/9 (11.1)	0/9 (0.0)	1/14 (7.1)	2/11 (18.2)
>9 months	0/10 (0.0)	2/17 (11.8)	1/24 (4.2)	0/22 (0.0)

Data shown are number of incident case participants of metabolic syndrome/number of individuals at risk within the specific interval (%).

Gunderson, et al. (2010). Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status: a 20-Year prospective study in CARDIA (Coronary Artery Risk Development in Young Adults). *Diabetes, 59(2), 495.*

Ma, S., Hu, S., Liang, H., Xiao, Y., & Tan, H. (2019). Metabolic effects of breastfeed in women with prior gestational diabetes mellitus: A systematic review and meta-analysis. *Diabetes Metab Res Rev, 35(3), e3108. doi:10.1002/dmrr.3108*

Supporting Systematic Reviews:

Tanase-Nakao, K., Arata, N., Kawasaki, M., Yasuhi, I., Sone, H., Mori, R., & Ota, E. (2017). Potential protective effect of lactation against incidence of type 2 diabetes in women with previous gestational diabetes mellitus : A systematic review and meta-analysis. *Diabetes Metab Res Rev.*

Pinho-Gomes, A. C., Morelli, G., Jones, A., & Woodward, M. (2021). Association of lactation with maternal risk of type 2 diabetes - a systematic review and meta-analysis of observational studies. *Diabetes Obes Metab. doi:10.1111/dom.14417*

Impact of lactation duration on development of T2DM @ 2yrs pp

8.79 % (5.47-12.11)

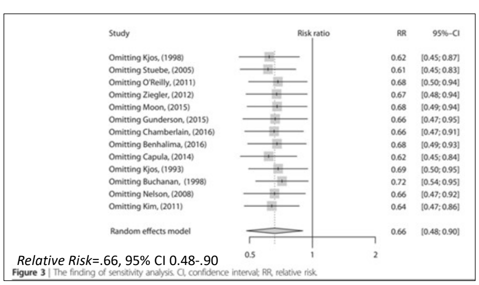
6.47% (4.11-8.83)

4.88% (3.37-6.39)

3.95% (2.07-5.83)

Gunderson 2015: Lactation and Progression to T2DM after Gestational Diabetes: A prospective cohort study

2018 Systematic Review & Meta-analysis of progression to T2 in lactation vs None

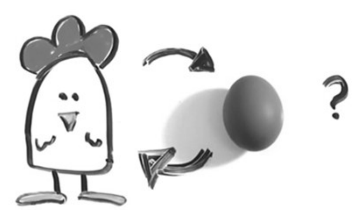


Relative Risk=.66, 95% CI 0.48-.90

Figure 3 | The finding of sensitivity analysis. CI, confidence interval; RR, relative risk.

But did not confirm impact of longer vs shorter lactation….

Feng, L., Xu, Q., Hu, Z., & Pan, H. (2018). Lactation and progression to type 2 diabetes in patients with gestational diabetes mellitus: A systematic review and meta-analysis of cohort studies. *J Diabetes Investig, 9(6), 1360-1369.*



Longer lactation → less obesity, metabolic problems

or reverse causality?

Metabolic Problems → Shorter lactation?

Asked: Stuebe, A. M. (2015). Does breastfeeding prevent the metabolic syndrome, or does the metabolic syndrome prevent breastfeeding?
Tested Hypothesis: Riddle, S. W., & Nommsen-Rivers, L. A. (2016). A Case Control Study of Diabetes During Pregnancy and Low Milk Supply.

Breastfeeding for Diabetes Prevention *Poudel 2016*

RECOMMENDATIONS:

Health education- benefits and barriers to breastfeeding
Integrated care of mother and child
Lactation and Endocrinology support
Proper breast exam
Lifestyle modifications
Medical nutrition therapy
Screening for complications
Overall comprehensive diabetes care
Awareness of potential drug interactions

"Early initiation and exclusive breastfeeding should therefore be highly encouraged and strongly supported."

Treatment Strategies: Address the underlying issue!

Management, weight loss, diet changes, supplements, medications

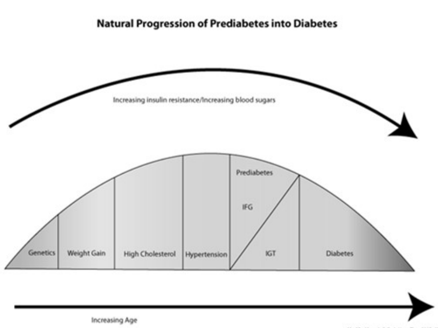
Forster, D. A., McEgan, K., Ford, R., Moorhead, A., Opie, G., Walker, S., & McNamara, C. (2011). Diabetes and antenatal milk expressing: a pilot project to inform the development of a randomised controlled trial. *Midwifery, 27(2), 209-214.*

Singh G; Chouhan R; Kidhu K. (2009). Effect of antenatal expression of breast milk at term in reducing breast feeding failures. *MJAFI*(65), 131-133.

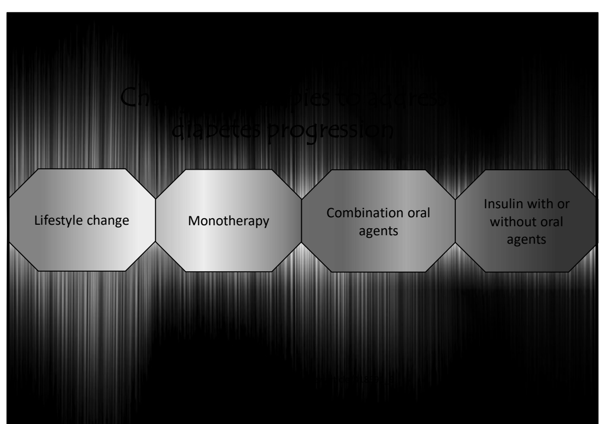
Most importantly…

Early frequent feeds to bring the milk in faster
Targeted prenatal-postnatal education reduced drop off

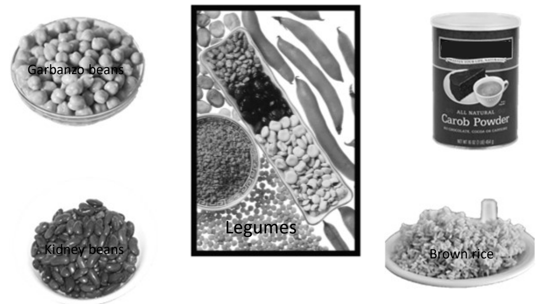
Chertok, I. R., & Sherby, E. (2016). Breastfeeding Self-efficacy of Women With and Without Gestational Diabetes.
Stuebe et al. (2016). A Cluster Randomized Trial of Tailored Breastfeeding Support for Women with GDM



http://www.priorslegh.co.uk/Diabetes/index.php/what-is-prediabetes



Smart Foods & Supplements for insulin resistance



http://www.ars.usda.gov/is/AR/archive/jul00/cinn0700.htm
Chemists Richard Anderson and Marilyn Polansky use high-performance liquid chromatography to identify compounds from cinnamon that improve the action of insulin. Photo by Peggy Greb.

Dietary supplements: Resveratrol

1500mg daily x 3 mos
- Total T ↓ 23%
- DHEAS ↓ 22%
- Fasting insulin ↓ 32%
- Insulin sensitivity index ↑66%

Banaszewska, B. (2016). Effects of Resveratrol on Polycystic Ovary Syndrome: A Double-blind, Randomized, Placebo-controlled Trial. *J Clin Endocrinol Metab,*

Dietary supplements: Gymnema

NEW RESEARCH:
300 mg twice daily for 12 weeks in patients with metabolic syndrome resulted in decreased body weight, BMI and very low-density lipoprotein (VLDL). Did not change insulin secretion or insulin sensitivity
Zuniga 2017

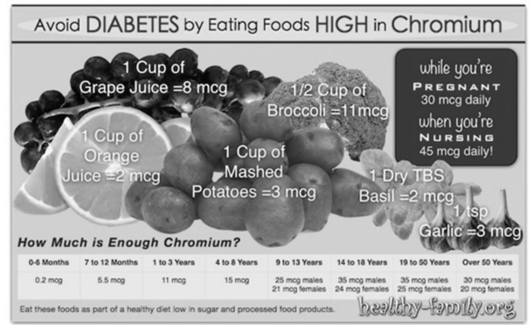
Dietary supplements: Calcium & Magnesium

Significantly improved Mg levels and insulin resistance in low-magnesium T2 subjects

Rodriguez-Moran, M., & Guerrero-Romero, F. (2003). Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care, 26(4), 1147-1152.*

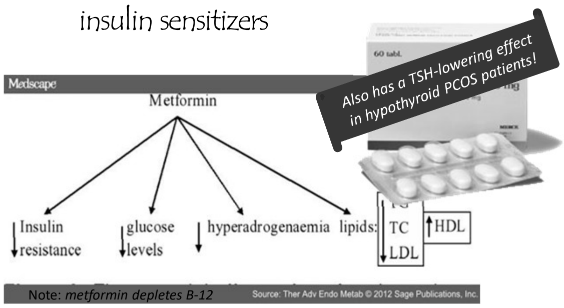
Bindlish, S., & Shubrook Jr, J. H. (2014). Dietary and Botanical Supplement Therapy in Diabetes. *Osteopathic Family Physician, 6(6).*

Dietary Supplements: Chromium



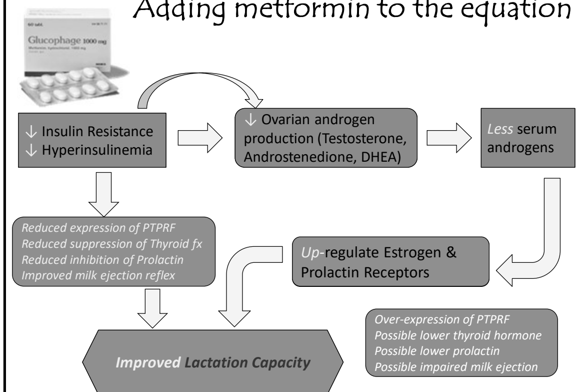
Bindlish, S., & Shubrook Jr, J. H. (2014). Dietary and Botanical Supplement Therapy in Diabetes. *Osteopathic Family Physician, 6(6).*

The Next Level: insulin sensitizers



Bargiota & Diamanti-Kandarakis. (2012) **The Effects of Old, New and Emerging Medicines on Metabolic Aberrations in PCOS.**
Lupoli et al. (2014). **Effects of treatment with metformin on TSH levels: a meta-analysis of literature studies.**

Adding metformin to the equation



Thanks to R. Craig, MD

Interesting Case study

-Measured output via infant transfer = 52mls/day

-Did *not* respond to domperidone @ 30 or 60mg

-Clinical indications of insulin resistance

Metformin: Transfer *increased 69%* to 88mls/day

McGuire, E., & Rowan, M. (2015). PCOS, breast hypoplasia and low milk supply: A case study. *Breastfeeding Review, 23(3), 29-32.*

New Case Study

McGuire, E., & Rowan, M. (2015). PCOS, breast hypoplasia and low milk supply: A case study. *Breastfeeding Review*

-Measured output via infant transfer = 52mls/day

-Did *not* respond to domperidone @ 30 or 60mg

-Clinical indications of insulin resistance

Metformin: Transfer *increased 69%* to 88mls/day

MALMS: Metformin to Augment Low Milk Production

Nommsen-Rivers 2019

Participants:
- 15 Mothers 1-8 weeks post birth, low supply, signs of IR
  - Median

Arms: (28 day treatment)
- Standard Care + Metformin, titrated 750mg to 2000mg
- Standard Care + Placebo

Results *(peaked @ 14d)*	**Max change in milk output mls/24 hrs**
Placebo n=5	-58 (-62 to -1)
Metformin ALL n=10	+8 (-23 to 33)
Metformin- 14-28 days (completers, n=8)	+22

"Strong negative association between signs of insulin resistance and baseline milk output"

Metformin during pregnancy?

Metformin reduces *(Tarry-Adkins 2021)*

✓*Gestational weight gain*
✓*Pre-eclampsia*
✓*Risk of hypertensive disorders* *(Racine 2021)*
✓*Hypoglycemia in infants* *(Skibinska 2021)*

Metformin vs Insulin *(Picon-Cesar 2021)*

✓ *Performed equally for OB outcomes*
✓ *Lower risk of hypoglycemic episodes*
✓ *Less gestational weight gain*
✓ *Improvements in PIH* *(Musa 2021)*

Tarry-Adkins, Ozanne, & Aiken. (2021). Impact of metformin treatment during pregnancy on maternal outcomes: a systematic review/meta-analysis.
Picón-César et al. (2021). MeDiGes Study. Metformin versus insulin in gestational diabetes: Glycemic control, and obstetrical and perinatal outcomes.

Metformin during pregnancy?

Pro's and Con's

- ❖ *Metformin concern: passes thru placenta, insulin doesn't→ higher weights in children*
- ❖ *Insulin concern: Impact on lactogenesis, infant suck*

Tarry-Adkins, Ozanne, & Aiken. (2021). Impact of metformin treatment during pregnancy on maternal outcomes: a systematic review/meta-analysis.
Picón-César et al. (2021). MeDiGes Study. Metformin versus insulin in gestational diabetes: Glycemic control, and obstetrical and perinatal outcomes.

Metformin & pregnancy breast growth

Retrospective 1 yr pp, n=186
PCOS patients (IR not confirmed)

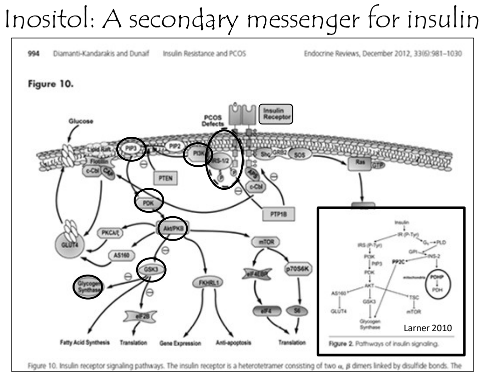
Looked at pre- to late-pregnancy bra sizes, Androgens

Results:
- No difference in breast increments between met and control
- Breast size change postively correlated w/ duration of bfg; BMI neg
- No correlations between DHEAS, T, FTI & br increment or duration
- Women w/ no changes more obese, high BP, shorter duration

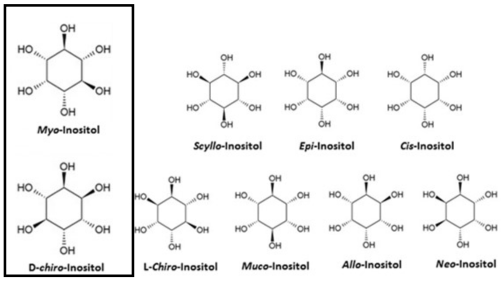
Vanky, et al (2012). Breast size increment during pregnancy and breastfeeding in mothers with polycystic ovary syndrome: a follow-up study of a randomised controlled trial on metformin versus placebo. *BJOG.*

The Second M

Inositol: A secondary messenger for insulin

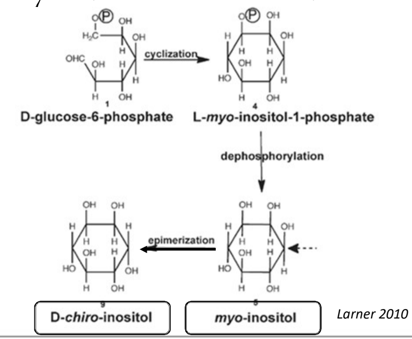


Inositol Glycans



Naturally occurring nutrient, type of sugar

Myo-inositol vs D-chiro-inositol



Larner 2010

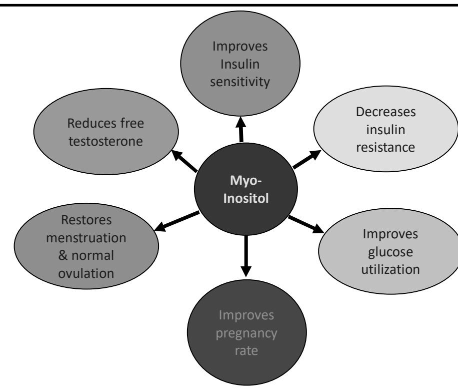
Figure 5. Conversion of D-glucose-6-phosphate to myo-inositol-1-phosphate by cyclization. Myo-inositol-1-phosphate is then dephosphorylated to myo-inositol, which then is converted by epimerization of the C3 hydroxyl (dashed left arrow) to DCI.

Larner 2010

Groups	Myo/chiro
Control	2.5
Type II diabetes patients	20.4
Nondiabetic relatives of type II diabetic patients	13.2
Type 1 diabetes patients	13.6

Insulin resistance is frequently associated with imbalance of Myo-I to D-chiro-I

⟶ *Caused by impaired conversion and/or increased urinary clearance of D-chiro-I*



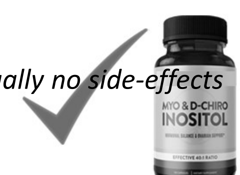
http://www.slideshare.net/LifecareCentre/what-is-40-1-in-management-of-dr-jyoti-agarwal-dr-sharda-jain-dr-jyoti-bhaskar

Another option?

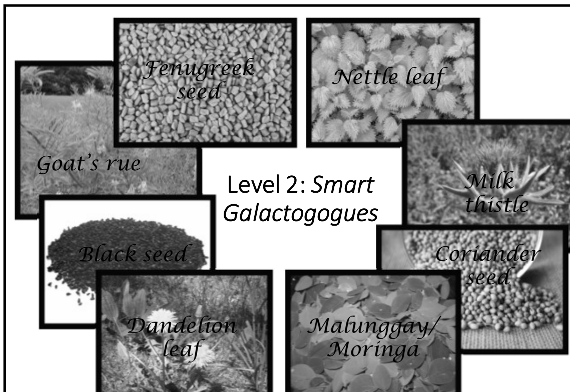
40:1

Myo D-chiro

Virtually no side-effects



Unfer 2014; Kalra 2016; Tahir 2019



Level 2: *Smart Galactogogues*